Amino Acid Catabolism

Amino Acids and Generating Energy

Proteins can be used as fuel for **skeletal muscle cells**, and to a minor extent in hepatocytes, but mainly they are used in a similar way to fatty acids—**when glucagon dominant**, the liver will use the metabolites or end-products of amino acids for **gluconeogenesis** or for **ketogenesis**.

An amino acid that degrades to **acetoacetate**, **acetyl-CoA**, or **propionyl-CoA** is considered **ketogenic**. You may recognize these as substrates from lipid metabolism. Acetyl-CoA cannot be turned into glucose, though it can provide the NADH and $FADH_2$ to make ATP that gets the liver cell flush with energy to allow gluconeogenesis and ketogenesis.

An amino acid that degrades to **pyruvate** or **any other part of the TCA** is deemed to be **glucogenic**. All amino acids are **at least glucogenic**, except for lysine and leucine.

Some amino acids are **both ketogenic and glucogenic**.

KETOGENIC ONLY	GLUCOGENIC AND KETOGENIC	AT LEAST GLUCOGENIC
L-aminos	Aromatics – "Upper Left"	All others
Leucine	Phenylamine	Ala, Arg, Asp, Asn
Lycine	Tyrosine	Cystine
	Tryptophan	Glu, Gln, Gly
		His, Hydroxyproline
	Hard to Remember	Met, Pro
	Isoleucine	Ser, Val
	Threonine	

Table 20.1

Those that are **both glucogenic** and **ketogenic** are the **aromatics**, with an emphasis on tics. Phe, tyr, trp (the aromatics) then "emphasis on the tics" isoleucine and threonine.

Those that are **at least glucogenic** are **AxLL** amino acids, the pun being "ALL" "except" "lysine and leucine."

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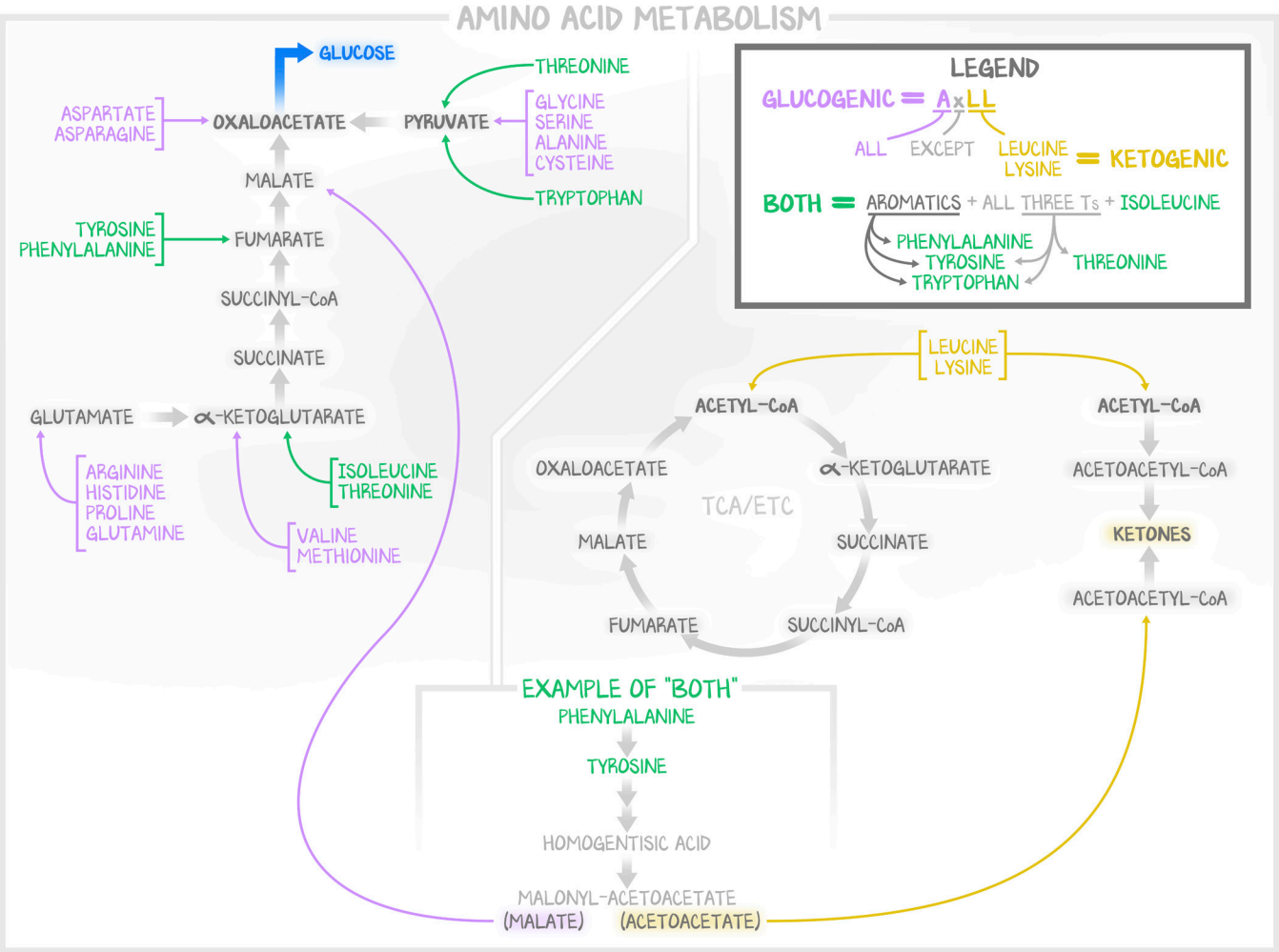

Figure 20.1: Amino Acid Metabolism

Disorders of Amino Metabolism: PKU

The first deficiency, known as **phenylketonuria (PKU)**, is caused by a deficiency of **phenylalanine hydroxylase** that turns phenylalanine to tyrosine. This is the highest-yield in terms of being asked questions. PKU is part of the **prenatal genetic screen**. The problem has two parts. The first is that **everything we eat, every amino acid source, has phenylalanine**. When there's an inability to process it, there's an accumulation of it, which leads to **intellectual disabilities**. A diet to prevent this is absurdly restrictive. It relies on fruits, vegetables, breads, and pasta to maintain enough amino acids to actually grow (too little protein and the child develops intellectual disabilities) and a limited amount of amino acids to prevent accumulation (which also causes intellectual disabilities). Also in the presentation should be a **musty odor**.

The second problem is that not only does phenylalanine accumulate, but also **tyrosine doesn't get made**. Tyrosine is critical for the production of melanin, which gives our skin pigment. Therefore, these kids are **pale-haired**, **pale-skinned** and develop crippling developmental problems.

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The good news is that once they reach adulthood (their brain is already developed), excess phenylalanine doesn't cause much trouble. It is only harmful **in utero** (mothers with PKU must adhere to the diet **while pregnant** even if the fetus is known to be unaffected) and in childhood (kids with PKU must adhere to the diet). It is **autosomal recessive** and rare enough that almost never do mom and baby both have the disease.

Disorders of Amino Metabolism: Albinism

Tyrosine, in a divergent pathway from metabolism, is responsive for **melanin** production through **tyrosinase**. In severe forms, there is no melanin anywhere, leading to white skin, hair, and nails. Various penetrance means that affected individuals may simply be fair-haired and fair-skinned, with a massively increased risk of skin cancer and sensitivity to UV light. Avoidance of the sun is key.

Disorders of Amino Metabolism: Alkaptonuria

As we approach the end of aromatic metabolism, a deficiency in **homogentisic acid oxidase** causes an accumulation of **homogentisic acid**. This acid is fairly **silent**. It deposits in the **joints**, especially large joints like hips and vertebrae. Because of this, patients require **joint replacement earlier than expected** to remain active. During the procedure, **ochronosis** (dark cartilage) is found. The other way this condition is diagnosed is as an incidental finding on an autopsy. When compared to the severe developmental problems of PKU, alkaptonuria is fairly benign. It is pathognomically accompanied by dark urine. Homogentisic acid is simply darkly pigmented, and deposits in urine and joints.

Disorders of Amino Metabolism: Maple Syrup Urine Disease

Transitioning to the upper right, we see that **leucine** can become acetyl-CoA (ketogenic) while **valine** (glucogenic) and **isoleucine** (both) can become **propionyl-CoA** (odd-chain fatty acids). These three amino acids are branched-chain amino acids and must all use **branched-chain ketoacid dehydrogenase**. However, the deficiency of this dehydrogenase does not result in the expected disease phenotype—it isn't a compromise of keto, gluco, and both.

Maple syrup urine disease is characterized by a **sweet odor to the urine**. Accumulation of branched-chain amino acids leads to **mental retardation**, muscle weakness, and death. There will also be an associated **ketoacidosis** from loss of glucogenic pathways. Restriction of valine, leucine, and isoleucine is the only treatment. Even though we lose ketogenic and glucogenic pathways, the symptomatology is hypoglycemia and increased ketosis.

Disorders of Amino Metabolism: Homocystinuria

The bottom of the image is way complex, and we've simplified it down hardcore. The key thing to see here is that **VOMIT** will enter the Krebs cycle as succinyl-CoA, meaning they are glucogenic. VOMIT refers to the **valine** (Branched-chain), **odd-chain** fatty acid (entering as proprionyl-CoA), **methionine** (SAM cycle at the bottom), **isoleucine** (not depicted), and **threonine** entering somewhere between cystathione and proprionyl-CoA. I don't know why VOMIT is a thing, or how it helps, but it has been perpetuated in so many review resources, I felt compelled to include it.

Because there is so much going on in this pathway, we need to parse it down. The SAM cycle happens. Familiar or not, what actually matters is the result of the SAM cycle, not the process. At the end of the SAM cycle, **homocysteine** exits the cycle and heads toward succinyl-CoA. If there is a deficiency of **cystathionine synthase**, homocysteine levels rise, giving us **homocystinuria**. This is super rare, but has a very classic presentation of **venous clots** (deep-vein thrombosis) and **arterial clots** (strokes) with **accelerated atherosclerosis**. It also presents with marfanoid features and mental retardation, but the elevated levels of homocysteine lead to weird clotting disorders and inflammatory vessel disease not seen in other named diseases above.

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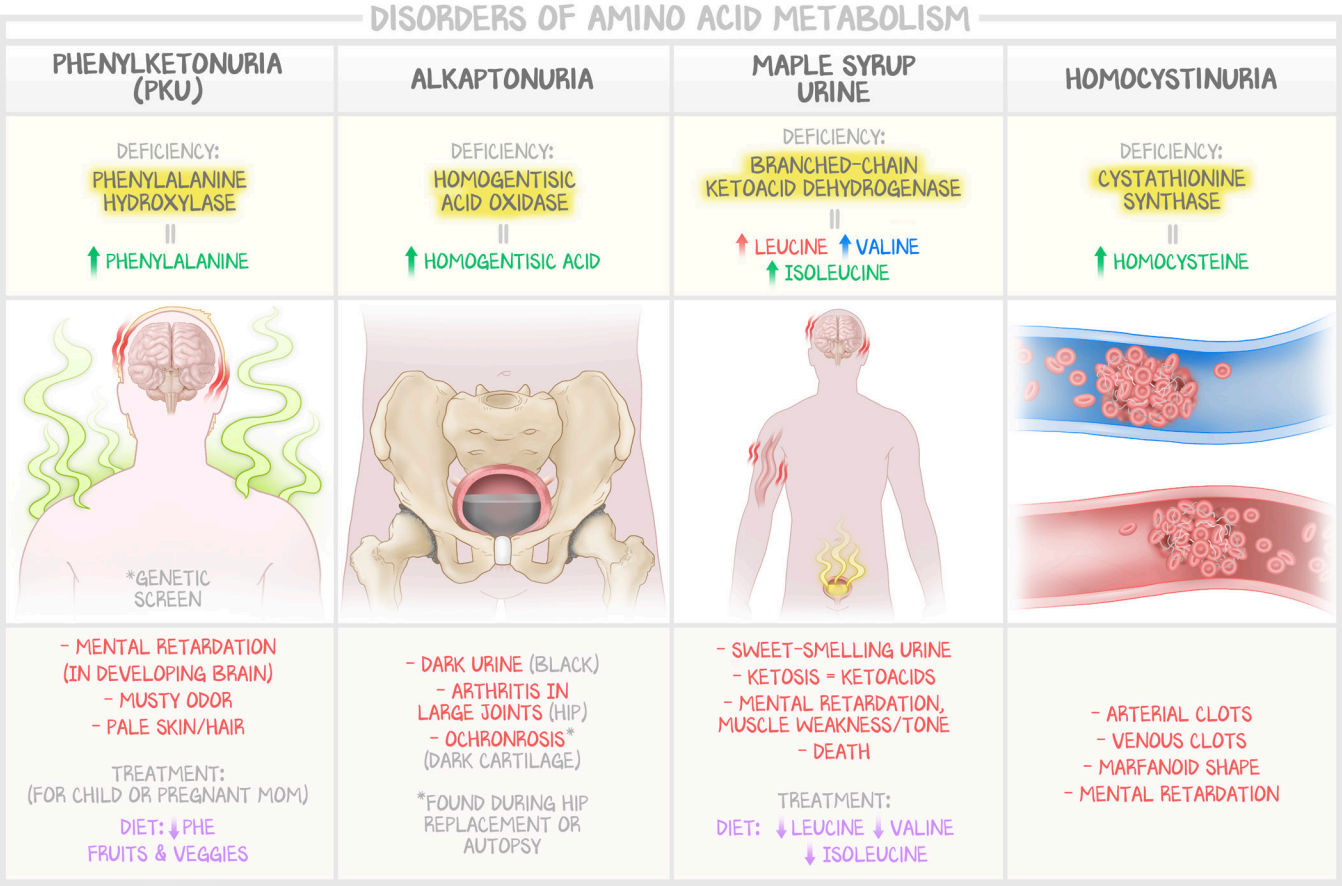

Figure 20.2: Disorders of Amino Acid Metabolism

Disorders of Amino Metabolism: B_{12} Deficiency and Folate Deficiency

This is a hot topic because its difference is so clean clinically and so important in treatment. We see that **B_{12}** is required for both the final step of **methylmalonic acid** to **succinyl-CoA**. If you have B_{12} deficiency, there will be **elevated methylmalonic acid**. This is a key difference between B_{12} deficiency and folate deficiency.

Where they share metabolism is in the **SAM cycle**. Homocysteine to **methionine** is responsible for regeneration of **Tetro›hydro-FOLATE**. So we need folate to be tetro-hydro'd and we need B_{12} to make that reaction go. If it doesn't, **homocysteine levels rise**. We've seen what happens with homocysteinuria, only B_{12} and folate are nutritional deficiencies that cause anemia later in life, not developmental delays.

The type of anemia they cause is a **megaloblastic anemia** characterized by **multisegmental neutrophils** and **macrocytic anemia**. Both are a result of insufficient material for DNA synthesis (the methionine). Both cause a large MCV. Both cause megaloblastic anemia. Both cause homocysteine levels to rise. But **only B_{12} deficiency also causes methylmalonic acid to rise** and **only B_{12} deficiency can cause permanent neurological impairment**. You also learn in the Step 2 content how to separate these two disorders based on the presentation (B_{12}—pernicious anemia and a decade of deficiency; folate—tea-and-toast diet and a month of deficiency) and how, when it comes down to it, the **methylmalonic acid** can separate the two if the values of B_{12} and folate are equivocal.

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